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# Prognostic value of tumor necrosis at CT in diffuse large B-cell lymphoma

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ABSTRACT

*Objective:* To determine the prognostic value of tumor necrosis at computed tomography (CT) in newly diagnosed diffuse large B-cell lymphoma (DLBCL).
*Materials and methods:* This retrospective study included 51 patients with newly diagnosed DLBCL who had undergone both unenhanced and intravenous contrast-enhanced CT before R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisolone) chemo-immunotherapy. Presence of tumor necrosis was visually and quantitatively assessed at CT. Associations between tumor necrosis status at CT and the National Comprehensive Cancer Network (NCCN) International Prognostic Index (IPI) factors were assessed. Cox regression analysis was used to determine the prognostic impact of NCCN-IPI scores and tumor necrosis status at CT.
*Results:* There were no correlations between tumor necrosis status at CT and the NCCN-IPI factors categorized age ($\rho = -0.042$, $P = 0.765$), categorized lactate dehydrogenase (LDH) ratio ($\rho = 0.201$, $P = 0.156$), extranodal disease in major organs ($\varphi = -0.245$, $P = 0.083$), Ann Arbor stage III/IV disease ($\varphi = -0.208$, $P = 0.141$), and Eastern Cooperative Oncology Group (ECOG) performance status ($\varphi = 0.015$, $P = 0.914$). In the multivariate Cox proportional hazards model, only tumor necrosis status at CT was an independent predictive factor of progression-free survival ($P = 0.003$) and overall survival ($P = 0.004$).
*Conclusion:* The findings of this study indicate the prognostic potential of tumor necrosis at CT in newly diagnosed DLBCL.



## 1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for 30–35% of cases [1]. Despite overall improvements in outcomes of DLBCL, particularly with the advent of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisolone) chemo-immunotherapy, approximately one-third of patients still develop relapsed/refractory disease that remains a major cause of morbidity and mortality [2]. Early identification of patients who will experience relapsed/refractory disease is of importance, because this will allow for the noninitiation or early discontinuation of ineffective standard front-line R-CHOP therapy, and provide a timely opportunity to switch to potentially more effective therapies. The International Prognostic Index (IPI) and its successors R-IPI and NCCN-IPI allow for risk stratification [3–5], but are insufficiently accurate to identify those patients in whom R-CHOP chemo-immunotherapy is likely going to fail. There is an active search for new prognostic biomarkers in DLBCL [1,2].

Imaging plays an important role in the evaluation of diffuse large B-cell lymphoma, and is done by means of computed tomography (CT), either as CT alone or in combination with $^{18}$F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET/CT) [6]. In the pretreatment setting, the main role of imaging is to detect and define the extent of disease for Ann Arbor staging and subsequent therapy response assessment. However, imaging findings may potentially also be useful to identify patients who are suffering from treatment-resistant DLBCL subtypes. CT scans of patients with

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DLBCL sometimes show tumor necrosis. Tumor necrosis shown at CT may indicate that the underlying DLBCL has an aggressive tumor growth. However, it is still unknown whether this phenomenon has any prognostic implications in DLBCL.

The purpose of this study was to determine the prognostic value of tumor necrosis at CT in newly diagnosed DLBCL patients who are treated with R-CHOP chemo-immunotherapy.

## 2. Materials and methods

### 2.1. Study design and patients

Local institutional review board approval was obtained for this retrospective study, and the requirement for written informed patient consent was waived. Any patient presenting with newly diagnosed DLBCL routinely undergoes pretreatment FDG-PET/CT at our institution. The hospital's database was searched for all patients with newly diagnosed DLBCL, who presented between September 2007 and December 2013. Inclusion criteria for this study were: newly diagnosed and histologically proven DLBCL, availability of both non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT from skull base to upper thigh as part of the same FDG-PET/CT examination that was performed on the same day, availability of blind bone marrow biopsy (BMB) of the posterior iliac crest and serum lactate dehydrogenase (LDH) measurement, and treatment with R-CHOP chemo-immunotherapy. Exclusion criteria for this study were: primary mediastinal DLBCL (which is recognized as a separate disease entity), previously treated/relapsed lymphoma, transformed lymphoma, coexistence of a second lymphoma subtype in the diagnostic biopsy, another cancer within the past five years, start of therapy before FDG-PET/CT.

### 2.2. Image acquisition

Non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT were acquired as part of an FDG-PET/CT examination, using a 40-detector row PET/CT system (Biograph 40 TruePoint PET/CT, Siemens Healthcare). Patients ingested a radio-opaque oral CT contrast agent (Telebrix Gastro, Guerbet) and fasted for 6 h before receiving 3 MBq/kg body weight of FDG intravenously. Sixty minutes after FDG injection, low-dose CT images from skull base to upper thigh were acquired using the following settings: 120 kV, 26–30 mAs (automatic dose modulation), 0.8-s tube rotation time, pitch of 1.2, and 1.5-mm slice width (reconstructed to contiguous 5-mm axial slices to match the slice thickness of the PET images). PET scanning was performed from mid femur to base of skull in five or six bed positions, with 3 min per bed position. Non-intravenous contrast-enhanced low-dose CT data were used for PET attenuation correction. PET images were reconstructed with an ordered-subsets expectation maximization algorithm for 14 subsets and four iterations. The image reconstruction matrix was 128 × 128. Finally, a non-ionic iodinated contrast agent (Xenetix 300, Guerbet; 3 mL/s with bolus tracking) was administered intravenously, and full-dose CT from skull base to midthigh was performed in the portal venous phase using the following settings: 120 kV, 60–160 mAs (automatic dose modulation), 0.8-second tube rotation time, pitch of 1.2, and 1.5-mm slice width.

### 2.3. Image interpretation

An experienced reader (T.C.K.) evaluated the combination of non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT for the presence of tumor necrosis. The reader was blinded to clinical and laboratory findings, findings of other imaging modalities, BMB findings, and patient outcome. Lymph nodes with a short-axis diameter exceeding 10 mm in the axial plane were considered positive for lymphoma. Any area of abnormal attenuation or mass in extranodal organs was also considered positive for lymphoma. Splenomegaly (i.e. splenic index exceeding 725 $cm^3$ [7]) was considered positive for lymphoma, but hepatomegaly without any focal liver lesions was not. Tumor necrosis was considered present if low-attenuation areas were visually identified in nodal or extranodal lymphomatous sites with corresponding Hounsfield units (HU) measuring between 10 and 30 Hounsfield units [8], and without any (relevant) HU increase (up to a maximum of 5 HU) between non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT images, as determined by region of interest analysis (ROI) (Figs. 1 and 2). Size-adjustable oval-shaped ROIs were used for this purpose. Sites of necrosis and corresponding HU values measured in the center of the necrotic area at intravenous contrast-enhanced full-dose CT were recorded.

### 2.4. National Comprehensive Cancer Network (NCCN) International Prognostic Index (IPI)

Age, serum LDH levels, presence of extranodal disease in major organs (either bone marrow, central nervous system, liver/gastrointestinal tract or lung), presence of Ann Arbor stage III/IV disease, and Eastern Cooperative Oncology Group (ECOG) performance status score of each patient were recorded, at time of diagnosis, in order to calculate an NCCN-IPI score, as described previously [5]. The four NCCN-IPI risk groups (low [scores 0–1], low-intermediate [scores 2–3], high-intermediate [scores 4–5] and high [scores 6–8]) were then dichotomized into low risk (including low and low-intermediate risk) and high risk (including high-intermediate and high risk) groups.

### 2.5. Patient follow-up

Clinical follow-up and follow-up FDG-PET/CT were used in all patients to determine if and when relapsed or progressive disease had occurred during follow-up, according to the Revised Response Criteria for Malignant Lymphoma [9]. Progression-free survival (PFS) was calculated from the date of diagnosis to documented disease relapse/progression or, for patients dying as a result of causes unrelated to DLBCL or the lymphoma treatment, the date of death. For surviving patients who did not experience disease relapse/progression, follow-up was censored at the date the patient was last known to be alive. Overall survival (OS) was calculated from the date of diagnosis until death as a result of any cause or, in surviving patients, censored at the date last known to be alive.

### 2.6. Statistical analysis

Associations between tumor necrosis status at CT (i.e. tumor necrosis absent or present) and the NCCN-IPI factors categorized age (>40–60, >60–75, and >75 years), categorized LDH ratio (>1–3 or ≥3 upper limit of normal), presence of extranodal disease in major organs (either bone marrow, central nervous system, liver/gastrointestinal tract or lung), presence of Ann Arbor stage III/IV disease, and ECOG performance status (≥2) were assessed using Spearman ($\rho$) (for ordinal NCCN-IPI factors) or Phi ($\varphi$) (for binary NCCN-IPI factors) correlation coefficient analyses.

PFS and OS were assessed using the Kaplan–Meier method with log-rank test [10], according to tumor necrosis status at CT (tumor

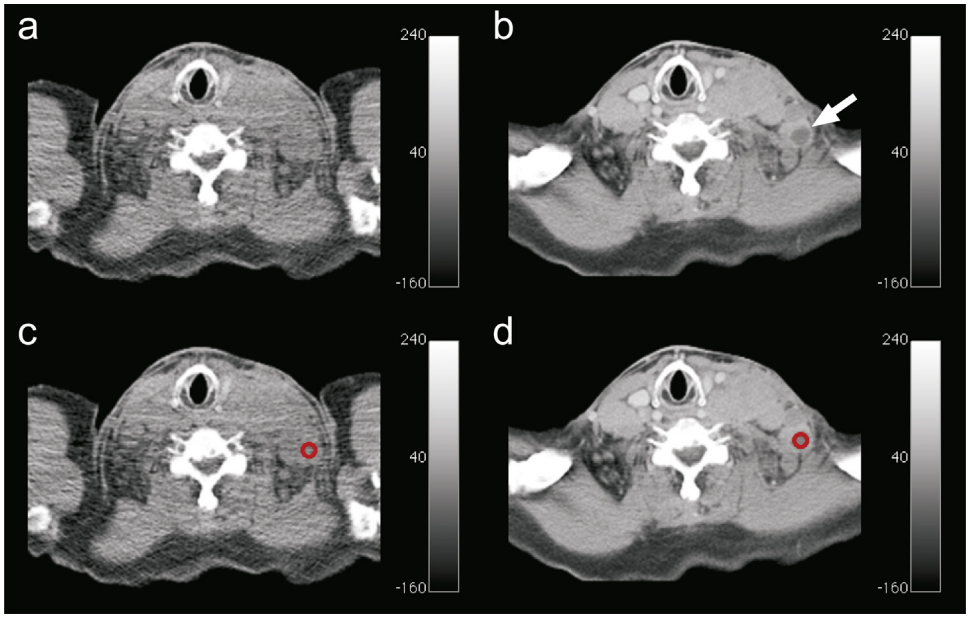


**Fig. 1.** Example of tumor necrosis at CT in a 64-year-old man with newly diagnosed DLBCL. Axial non-intravenous contrast-enhanced low-dose CT (a and c) and intravenous contrast-enhanced full-dose CT (b and d) at the level of the lower neck, before (a and b) and after (c and d) ROI placement for HU measurement. Contrast-enhanced full-dose CT shows a left-sided pathologically enlarged cervical lymph node with central hypoattenuation (b, arrow), suggestive of necrosis in a lymphomatous lymph node. HU value of the central hypoattenuating area in this lymph node was 13.8 before and 13.9 after intravenous contrast administration, indicating non-enhancement and confirming the presence of necrosis.

necrosis absent vs. tumor necrosis present) and dichotomized NCCN-IPI risk groups (low risk vs. high risk). Finally, univariate and multivariate Cox regression analyses were performed for tumor necrosis status at CT and dichotomized NCCN-IPI risk groups. All tests were two-sided and *P*-values less than 0.05 were considered to indicate a significant difference.

Statistical analyses were executed using Statistical Package for the Social Sciences version 17.0 (Chicago, Illinois, USA) and MedCalc statistical software version 12.6.0 (Ostend, Belgium).

## 3. Results

### 3.1. Patients

A total of 121 patients presented with newly diagnosed and histologically proven DLBCL, between September 2007 and December 2013, and were potentially eligible for inclusion. Of these 121 patients, 2 patients were excluded because of primary mediastinal DLBCL, 4 patients were excluded because of previously

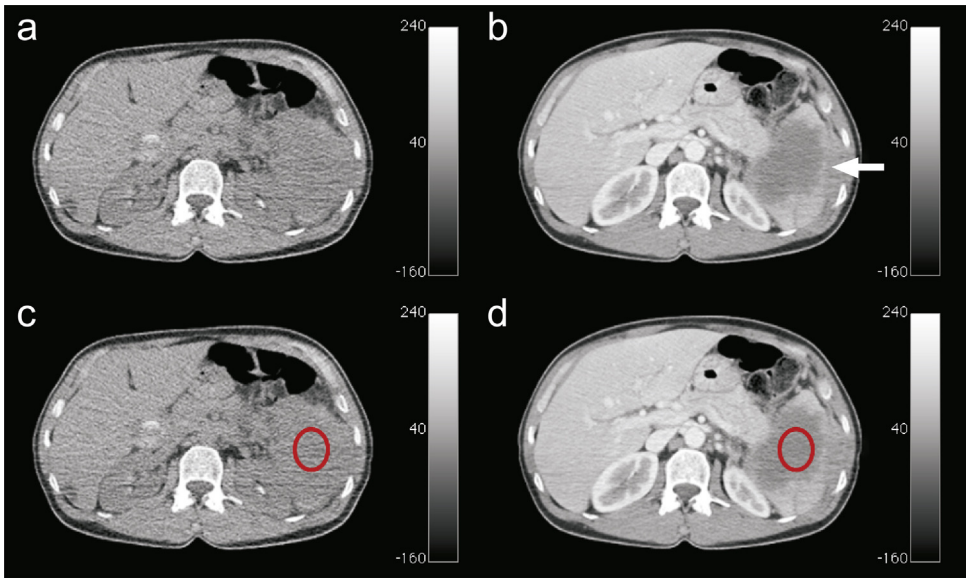


**Fig. 2.** Example of tumor necrosis at CT in a 49-year-old woman with newly diagnosed DLBCL. Axial non-intravenous contrast-enhanced low-dose CT (a and c) and intravenous contrast-enhanced full-dose CT (b and d) at the level of the upper abdomen, before (a and b) and after (c and d) ROI placement for HU measurement. Contrast-enhanced full-dose CT shows a large hypoattenuating area in the spleen (b, arrow), suggestive of necrosis in a lymphomatous spleen. HU value of the hypoattenuating area in the spleen was 24.8 before and 24.6 after intravenous contrast administration, indicating non-enhancement and confirming the presence of necrosis.

**Table 1**
Characteristics of included patients.

| | Tumor necrosis at CT | No tumor necrosis at CT |
|---|---|---|
| Patients (no.) | 7 | 44 |
| *Age* | | |
| Mean ± SD (years) | 66.6 ± 10.6 | 65.8 ± 11.3 |
| Median (years) | 69.0 | 66.5 |
| Range (years) | 49–81 | 28–84 |
| Male/female | 5/2 | 27/17 |
| **NCCN-IPI factors** | | |
| *Age* | | |
| ≤40 years | 0 | 1 |
| >40 to ≤60 years | 2 | 11 |
| >60 to ≤75 years | 4 | 22 |
| >75 years | 1 | 10 |
| ECOG PS > 1 | 1 | 7 |
| *LDH > ULN* | | |
| ≤1 | 0 | 15 |
| >1 to ≤3 | 6 | 23 |
| >3 | 1 | 6 |
| Stage III/IV | 5 | 40 |
| Major extranodal involvement[a] | 2 | 28 |
| *NCCN-IPI score* | | |
| Low risk (0–1) | 0 | 1 |
| Low-intermediate risk (2–3) | 1 | 9 |
| High-intermediate risk (4–5) | 6 | 22 |
| High risk (≥6) | 0 | 12 |
| *Follow-up time of surviving patients* | | |
| Mean ± SD (days) | 423 ± 372 | 1045 ± 624 |
| Median (days) | 423 | 964 |
| Range (days) | 159–686 | 134–2386 |
| Disease relapse or progression, or death (no.) | 5 | 11 |
| Death (no.) | 5 | 9 |

*Abbreviations*: ECOG PS: Eastern Cooperative Oncology Group Performance Score; LDH: lactate dehydrogenase; NCCN-IPI: National Comprehensive Cancer Network International Prognostic Index; SD: standard deviation; ULN: upper limit of normal (according to the local reference values of each participating institution).

[a] Defined as either bone marrow, central nervous system, liver/gastrointestinal tract or lung involvement, with histological confirmation of bone marrow and central nervous system involvement, as recommended by Zhou et al. [5].

treated/relapsed lymphoma, 14 patients were excluded because of a transformed lymphoma, 6 patients were excluded because of coexistence of a second lymphoma subtype in the diagnostic biopsy, 2 patients were excluded because of another cancer within the past five years, 25 patients were excluded because of non-availability of intravenous contrast-enhanced full-dose CT from skull base to upper thigh performed with use of the same PET/CT system as non-intravenous contrast-enhanced low-dose CT on the same day, 12 patients were excluded because of absence of BMB, and 5 patients were excluded because of no or other treatment than R-CHOP chemo-immunotherapy. Thus, 51 patients (32 men and 19 women, mean age: 65.9 years, age range: 28–84 years) were finally included. Detailed patient characteristics are shown in Table 1.

### 3.2. Tumor necrosis at CT

Tumor necrosis at CT was identified in 7 of 51 (13.7%) patients, and was located in the left cervical lymph nodes ($n = 1$), right axillary lymph nodes ($n = 1$), mesenteric lymph nodes ($n = 1$), paraaortal lymph nodes ($n = 1$), spleen ($n = 2$), and pelvic tumor mass ($n = 1$). Measured HU values of tumor necrosis ranged between 13.9 and 24.6 (mean ± standard deviation: 21.4 ± 3.5).

### 3.3. Follow-up

The median follow-up time of surviving patients was 1011 days (range: 134–2386 days). In total, 16 patients (31.4%) experienced disease relapse/progression or death, and 14 patients (27.5%) died.

### 3.4. Prognostic performance of tumor necrosis status at CT

There were no correlations between tumor necrosis status at CT and the NCCN-IPI factors categorized age ($\rho = -0.042$, $P = 0.765$) categorized LDH ratio ($\rho = 0.201$, $P = 0.156$), presence of extranodal disease in major organs ($\varphi = -0.245$, $P = 0.083$), presence of Ann Arbor stage III/IV disease ($\varphi = -0.208$, $P = 0.141$), and ECOG performance status ($\varphi = 0.015$, $P = 0.914$).

Five of seven (71.4%) patients with tumor necrosis died during follow-up, 3 because of treatment-resistant DLBCL, 1 because of relapsed DLBCL and 1 because of treatment-related complications. Patients with tumor necrosis at CT had significantly worse PFS and OS than patients without tumor necrosis at CT (log-rank test, $P = 0.001$ and $P = 0.001$, respectively) (Fig. 3). On the other hand, there were no significant differences in PFS and OS between low risk and high risk NCCN-IPI groups (log-rank test, $P = 0.100$ and $P = 0.171$, respectively) (Fig. 4). Univariate Cox regression analysis showed that only tumor necrosis status at CT was a significant predictor of both PFS and OS ($P = 0.003$ and $P = 0.004$, respectively), whereas dichotomized NCCN-IPI risk group was not ($P = 0.135$ and $P = 0.203$, respectively). In the multivariate Cox proportional hazards model, only tumor necrosis status ($P = 0.003$ and $P = 0.004$, respectively) was an independent predictive factor of PFS and OS (Table 2).

## 4. Discussion

The results of this study indicate that tumor necrosis at CT may be used as an imaging biomarker for assessing prognosis in newly diagnosed DLBCL patients who are treated with R-CHOP chemo-immunotherapy. Patients with tumor necrosis at CT had

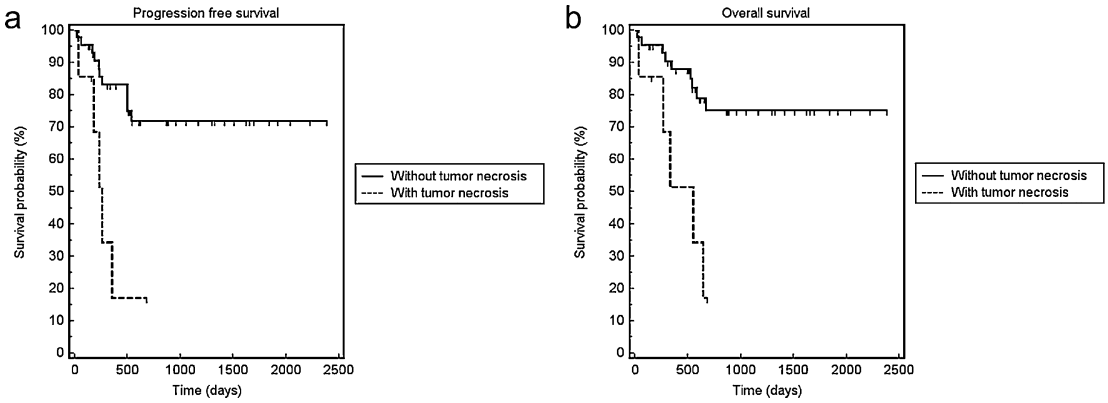


**Fig. 3.** Kaplan–Meier curves for PFS (a) and OS (b) of patients with tumor necrosis at CT vs. patients without tumor necrosis at CT. Patients with tumor necrosis at CT had significantly worse PFS and OS than patients without tumor necrosis at CT (log-rank test, $P = 0.001$ and $P = 0.001$, respectively).

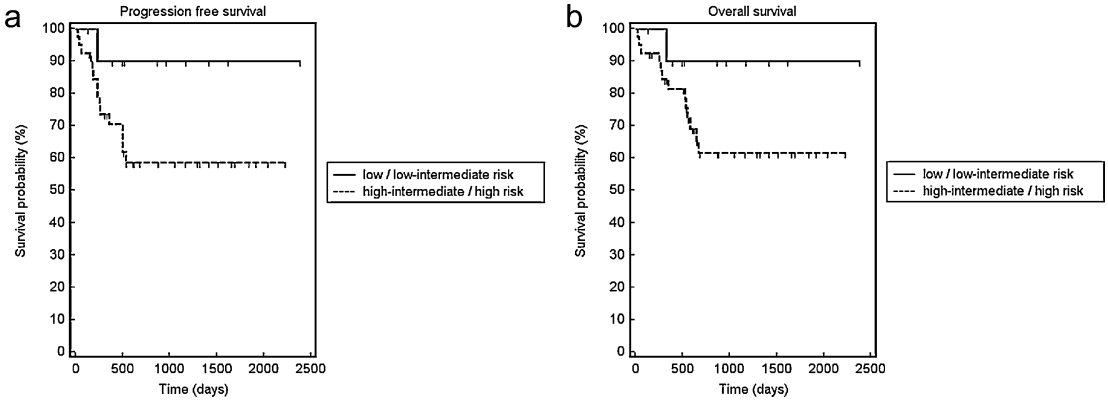


**Fig. 4.** Kaplan–Meier curves for PFS (a) and OS (b) of patients with low risk NCCN-IPI scores vs. high risk NCCN-IPI scores. There were no significant differences in PFS and OS between low risk and high risk NCCN-IPI groups (log-rank test, $P = 0.100$ and $P = 0.171$, respectively).

a significantly worse outcome in terms of both PFS and OS than those without tumor necrosis at CT. Tumor necrosis status at CT was found not to be associated with any of the established NCCN-IPI factors, including age, LDH ratio, presence of extranodal disease in major organs, presence of Ann Arbor stage III/IV disease, and ECOG performance status, indicating that it can be used as an independent prognostic factor. Interestingly, tumor necrosis status at CT even outperformed the dichotomized NCCN-IPI risk stratification in this study. Although the relatively low sample size of this study may explain the lack of prognostic value of the NCCN-IPI, it signifies the prognostic potential of tumor necrosis status at CT. In addition, it should be realized that current risk stratification indices, including the NCCN-IPI [3–5], are insufficiently accurate to identify the one-third of DLBCL patients who will develop relapsed/refractory disease [2]. Given the fact that CT is routinely performed in most patients with newly diagnosed DLBCL, this new imaging biomarker is readily available and does not result in additional costs.

Two previous studies have investigated the prognostic implications of tumor necrosis at CT in lymphoma [8,11]. In 1990, Hopper et al. [8] investigated chest CT scans of 76 patients with newly diagnosed Hodgkin lymphoma with mediastinal involvement. CT scans showed necrotic lymph nodes in 16 (21%) patients. The difference between these patients and those without necrotic nodes was not statistically significant with respect to sex, age, stage, distribution of disease, presence of extranodal disease, cell type, mass diameter, or the presence of bulky disease. In addition, Kaplan–Meier analyses showed no differences between patients with necrotic mediastinal lymph nodes and those without, both with regard to their length of remission ($P = 0.35$) and their overall survival ($P = 0.25$). Hopper et al. [8] concluded that the presence of mediastinal necrotic lymph

**Table 2**
Cox regression analysis of progression free surival (PFS) and overall survival (OS).

| Characteristic | Univariate analysis PFS | | | Multivariate analysis PFS | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *P*-value | Hazard ratio | 95% CI | *P*-value |
| Tumor necrosis at CT vs. no tumor necrosis at CT | 5.079 | 1.725–14.957 | 0.003 | 5.079 | 1.725–14.957 | 0.003 |
| NCCN-IPI high risk vs. NCCN-IPI low risk | 4.682 | 0.625–35.095 | 0.135 | – | – | – |

| Characteristic | Univariate analysis OS | | | Multivariate analysis OS | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | Hazard ratio | 95% CI | Hazard ratio | 95% CI |
| Tumor necrosis at CT vs. no tumor necrosis at CT | 5.179 | 1.726–15.543 | 0.004 | 5.179 | 1.726–15.543 | 0.004 |
| NCCN-IPI high risk vs. NCCN-IPI low risk | 3.751 | 0.4953–28.410 | 0.203 | – | – | – |

nodes appears to have little prognostic significance in patients with newly diagnosed Hodgkin lymphoma. There are important differences between Hopper et al.'s study [8] and the present study. First, their study dealt with Hodgkin lymphoma [8], which has a more favorable prognosis than DLBCL [12]. Moreover, Hopper et al. [8] only evaluated mediastinal lymph nodes, whereas the present study evaluated both nodal and extranodal sites, from skull base to upper thigh. Furthermore, unlike Hopper et al.'s study [8], the present study used both non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT for the assessment of tumor necrosis, with non-enhancement as criterion for tumor necrosis. As has already been acknowledged by Hopper et al. [8], differentiation between necrosis and other causes of low-attenuation tumor areas (e.g. oedematous but viable tumor tissue) at intravenous contrast-enhanced CT only may be difficult. It should be noted that if the prognostic potential of tumor necrosis at CT is confirmed by future studies, both non-intravenous and intravenous contrast-enhanced CT may be considered necessary for pretreatment evaluation of DLBCL. This contradicts with the recommendations of recent studies that intravenous contrast-enhanced full-dose CT can be omitted from an FDG-PET/CT staging examination in lymphoma [13,14]. The recent development of integrated PET/magnetic resonance imaging might be an alternative strategy for determining whether necrotic lymph nodes are present or not, obviating the need for intravenous contrast-enhanced CT. However, sufficient data supporting this hypothesis are still lacking. In another study in 2001, Saito et al. [11] evaluated CT and MRI scans of 60 patients with different non-Hodgkin lymphoma subtypes for the presence or absence of spontaneous extensive necrosis in the lymphomatous nodes, before initiation of radiation or chemotherapy. Extensive necrotic lymph nodes were found in 15 (25%) patients. Patients with necrosis had significantly higher stages (Ann Arbor stage ≥II), greater IPI (≥2), and higher serum LDH levels than those without necrosis ($P = 0.001$, $P = 0.005$, and $P = 0.005$, respectively). Kaplan–Meier analyses for disease-free survival showed a significant difference for serum LDH levels ($P = 0.015$) and IPI ($P = 0.021$), but not for extensive necrosis ($P = 0.600$). Saito et al. [11] concluded that spontaneous extensive necrosis in lymphomatous nodes is not a rare event. In addition, they concluded that although this finding had no significant influence on disease-free survival in their small series of patients, spontaneous extensive necrosis may have a prognostic significance in patients with non-Hodgkin lymphomas [11]. The major limitation of Saito et al.'s study is the fact that different non-Hodgkin lymphoma subtypes (4 low-grade, 53 intermediate-grade, and 3 high-grade) were included and analyzed all together [11], although treatment and outcome of different non-Hodgkin lymphoma subtypes varies considerably [15]. In addition, Saito et al.'s study suffered from selection bias, because only patients referred for radiation therapy with or without chemotherapy were included [11]. Furthermore, Saito et al. [11] only evaluated for the presence of necrosis in lymph nodes and not in extranodal sites.

This study had several limitations. First, several patients who were potentially eligible for enrolment into this study had to be excluded, mainly because no intravenous contrast-enhanced full-dose CT was performed at the time of the FDG-PET/CT examination. This is due to the fact that these patients had already undergone intravenous contrast-enhanced full-dose CT before the FDG-PET/CT examination, because the diagnosis of DLBCL was not known yet. Although these patients had to be excluded to avoid any potential time-related difference in disease status between non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT, this is unlikely to have caused any selection bias. Second, because of the retrospective nature of this study, histopathological analysis of necrotic tumor sites at CT was not available. In the study by Saito et al. [11], histopathological analysis in 10 of 15 patients with necrotic lymph nodes showed that all the lymph nodes were completely involved with lymphomatous cells, including sinus and hila of the lymph nodes, and that almost all of the lymphomatous cells developed necrosis. Although the pathogenesis of tumor necrosis at CT in DLBCL remains unclear, it can be speculated that it indicates aggressive tumor growth with an apparent tendency for treatment resistance.

In conclusion, the findings of this study indicate the prognostic potential of tumor necrosis at CT in newly diagnosed DLBCL. Future prospective studies with larger sample sizes are required to validate the prognostic potential of this new imaging biomarker.

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## Conflict of interest

None declared.

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